Controlled study of DTIC versus DTIC plus epirubicin in metastatic malignant melanoma

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Summary

Forty-two previously untreated patients with metastatic malignant melanoma were randomized to receive DTIC at a dose of 250 mg/m²/day IV on days 1–5 or the same drug plus epirubicin (Epi-DX) at a dose of 90 mg/m² on day 1. Cycles were repeated every 3 weeks. Partial responses were observed in two out of 22 patients (9.1%) treated with DTIC, and in four out of 19 evaluable patients (21.1%) treated with Epi-DX + DTIC. Overall, Epi-DX + DTIC combination was well tolerated, thus permitting administration after a 3-week interval of the full drug dosages in all but two patients. No major cardiotoxicity was observed. Although patients in the Epi-DX + DTIC group had a better response rate than those in the DTIC group, the difference was not statistically significant, and the 21.1% response rate observed with the two-drug combination does not differ from that reported with DTIC used alone.

Introduction

At the present time, there are few effective chemo-therapeutic agents for treatment of patients with metastatic malignant melanoma. DTIC was reported to produce an objective response rate of 23.4% in 1188 evaluable patients (1), and because of the lack of other drugs or combinations yielding superior results, it can serve as a benchmark for other single and multidrug therapy regimens. Preliminary results from phase I-II studies with epirubicin (4’-epidoxorubicin, Epi-DX), one of new doxorubicin (DX) analogues, showed hints of activity in patients with renal carcinoma, rectal carcinoma and malignant melanoma, which are generally resistant to DX (2). Toxicity studies have also indicated that Epi-DX produces a pattern of acute toxicity similar to that of DX. However, Epi-DX was better tolerated than DX because of comparative lower incidence of vomiting, stomatitis, complete alopecia and severe myelosuppression (3). Studies performed in rodents bearing tumors showed that the combination of DX and DTIC is clearly synergistic in a variety of tumors, including B16 melanoma, with a minimal overlap in toxicity, so that almost the full doses of each drug can be used (4, 5). Gottlieb et al. (6) confirmed that the two drugs can also be used in man in nearly the full dosage with minimal toxicity complications, and an additive effect of DX and DTIC was found in the treatment of soft tissue sarcomas (7). Therefore, it was reasonable to think that also the toxicity of DTIC and Epi-DX given in combination would be non-additive, and a Phase I study performed at the Istituto Regina Elena of Rome demonstrated that the toxic effects associated with this regimen are the same as those expected with the single drugs used independently.

As a result, a controlled study was activated in order to evaluate the potential superiority of DTIC
and Epi-DX combination over DTIC alone in patients with metastatic malignant melanoma.

**Materials and methods**

Forty-two patients with histologically proven metastatic malignant melanoma entered in the study. Eligibility criteria included age 18–80 years, an estimated survival of at least 2 months, performance status ≥ 50 (Karnofsky scale), no history of congestive heart failure nor any evidence of ischemia or arrhythmias on EKG, no evidence of CNS metastases, an initial wbc count of ≥ 4000/mm³ and a platelet count ≥ 100 000/mm³, as well as adequate hepatic and renal function (bilirubin ≤ 1.5 mg/dl, creatinine ≤ 1.5 mg/dl), and informed consent. All patients were previously untreated with systemic chemotherapy and had measurable disease.

Pretreatment evaluation of patients included a complete history and physical examination, laboratory evaluation (complete blood count with platelet count and differential white blood count, liver function, serum creatinine, electrolytes, urinalysis), EKG, systolic time intervals (STI), and chest X-ray. Additional radiologic studies and scans were obtained when clinically indicated. Hemograms were analyzed on a weekly basis, blood chemistry tests and STI were repeated at a 3-week interval. An EKG was performed before each dose of Epi-DX and repeated after 24 h.

Before randomization to a treatment schedule, patients were stratified by site of metastases: metastases limited to soft tissues (skin, subcutaneous, lymph nodes), and visceral and/or osseous metastases (± soft tissue metastases). Twenty-two patients received DTIC 250 mg/m²/day by IV push for 5 consecutive days every 3 weeks. Twenty patients received DTIC as above plus Epi-DX 90 mg/m² on day 1 every 3 weeks. Epi-DX was supplied by Farmitalia as a red powder in 10 mg and 50 mg vials. The drug was reconstituted with sterile water at a concentration of 2 mg/ml and was administered by rapid IV injection. Drug dosages for subsequent treatments were modified as follows: if wbc count < 3999/mm³ and/or platelet count < 99 999/mm³, 50% of the dose was given; if wbc count < 2500/mm³ and/or platelet count < 75 000/mm³, treatment was delayed. Reduced doses of Epi-DX were given if the patient had an elevation of serum bilirubin > 1.5 mg/dl.

Response and toxicity were evaluated according to the WHO recommendations (8). An adequate trial required a minimum of two courses of chemotherapy.

**Results**

Forty-one of the 42 patients who entered the study received an adequate trial. One patient treated with Epi-DX+DTIC combination refused a second course of therapy after experiencing marked drug-related toxicity. This patient has been considered only for toxicity evaluation. The characteristics of the patients and response to therapy are summarized in Table 1. Two out of 22 patients (9.1%) allocated to DTIC group achieved a partial response, lasting 5 and 7 months, and one patient had a disease stabilization lasting 3 months. In the Epi-DX+DTIC group, 4 out of 19 patients (21.1%) had a partial response, lasting 9, 3, 8+ and 6+ months, respectively. Although this latter group fared somewhat better, there was no statistically significant difference in the response rate by treatment.

Table 2 shows the toxicities of the regimens. The toxic effects of DTIC were those usually encountered...